

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	45	FLECKENSTEIN NEAR BERNHARD	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:31
L3	10	NEIPEL FRANK	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/03/28 13:31
L4	6319	(HHV-8 or herpes\$10) and (interleukin-6 or IL-6 or V-IL-6 or vIL-6)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:40
L5	111	(HHV-8 or herpes\$10) WITH (interleukin-6 or IL-6 or V-IL-6 or vIL-6)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:34
L6	7	(HHV-8 or herpes\$10) NEAR (interleukin-6 or IL-6 or V-IL-6 or vIL-6)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:33
L7	5	((HHV-8 or herpes\$10) WITH (interleukin-6 or IL-6 or V-IL-6 or vIL-6)).clm.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:35
L9	13	ALBRECHT NEAR JENS-CHRISTIAN	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:36
L11	275	Chang Yuan	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	OFF	2005/03/28 13:37
L12	20	Hayward Gary	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	OFF	2005/03/28 13:38
L14	991	Nicholas John	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/03/28 13:39
L15	6	l11 and l5	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/03/28 13:40
L16	1	l12 and l5	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/03/28 13:40

L17	1	I14 and I5	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/03/28 13:40
L22	153	(interleukin-6 or IL-6 or V-IL-6 or vIL-6) NEAR (interleukin-6 or IL-6) NEAR receptor	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:43
L23	1	(V-IL-6 or vIL-6) NEAR (interleukin-6 or IL-6) NEAR receptor	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:44
L24	3	(V-IL-6 or vIL-6) SAME (interleukin-6 or IL-6) NEAR receptor	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:44
L25	21	(US-20030211468-\$ or US-20040228838-\$).did. or (US-5849564-\$ or US-5854398-\$ or US-5861240-\$ or US-5861500-\$ or US-6060284-\$ or US-6174685-\$ or US-6177080-\$ or US-6183751-\$ or US-6264958-\$ or US-6348586-\$).did. or (EP-524421-\$ or EP-893504-\$ or US-5854398-\$ or US-5861500-\$ or WO-9803657-\$ or WO-9416062-\$).did. or (JP-06113858-\$).did. or (US-5831064-\$ or US-6183751-\$ or WO-9803657-\$ or US-6264958-\$ or US-5831064-\$). did.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:51

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(FILE 'HOME' ENTERED AT 13:54:42 ON 28 MAR 2005)

FILE 'MEDLINE, CANCERLIT, CAPLUS, SCISEARCH' ENTERED AT 13:55:04 ON 28 MAR 2005

L1 288 S (VIRAL INTERLEUKIN-6) OR VIL-6 OR V-IL-6
L2 30089 S ((INTERLEUKIN-6 OR IL-6) (L) RECEPTOR) OR IL-6R
L3 111 S L1 (L) L2
L4 40 DUP REM L3 (71 DUPLICATES REMOVED)
L5 1 S L4 AND PY<=1996
L6 40 FOCUS L4 1-
E FLECKENSTEIN BERNHARD?/AU
L7 144 S E1
L8 3 S E2
L9 147 S L7 OR L8
L10 3 S L9 AND L3
L11 3 DUP REM L10 (0 DUPLICATES REMOVED)

=> d an ti so au ab pi l11 1-3

L11 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:89360 CAPLUS
DN 128:166368
TI The interleukin 6 of human herpesvirus 8 and its use in diagnostics and
therapeutics
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
IN Fleckenstein, Bernhard; Albrecht, Jens-Christian; Neipel, Frank;
Friedman-Kien, Alvin; Huang, Yao-Qi
AB Human herpesvirus 8 is found to carry a gene for an interleukin 6 that can
bind to the interleukin 6 receptor. The interleukin and the gene encoding
can be used in the diagnosis and treatment of a number of diseases including:
Kaposi sarcoma, Castleman's disease, multiple myeloma, kidney cell
carcinoma, mesangial proliferative glomerulonephritis or B cell lymphoma.
The protein may be manufactured by expression of the cloned gene.
PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 9803657 A1 19980129 WO 1996-EP3199 19960719
W: US
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
EP 912742 A1 19990506 EP 1996-927558 19960719
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, LU, NL, SE
US 2004228838 A1 20041118 US 2004-828343 20040421

L11 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:184856 CAPLUS
DN 128:293873
TI Human herpesvirus type 8 interleukin-6 homolog is functionally active on
human myeloma cells
SO Blood (1998), 91(6), 1858-1863
CODEN: BLOOAW; ISSN: 0006-4971
AU Burger, Renate; Neipel, Frank; Fleckenstein, Bernhard; Savino,
Rocco; Ciliberto, Gennaro; Kalden, Joachim R.; Gramatzki, Martin
AB Seroepidemiol. and polymerase chain reaction studies have strongly
suggested that human herpesvirus type 8 (HHV-8) is associated with Kaposi's
sarcoma, Castleman's disease, and body cavity-based lymphoma. The genome
of HHV-8 harbors a viral analog of the interleukin-6 (IL-6) gene. The amino acid sequence of the viral
IL-6 (vIL-6) protein is 24.7% identical to human IL-6 (hIL-6). IL-6 as a B-cell growth and differentiation factor is known to play
an essential role in the pathophysiol. of B-cell tumors. Thus, it seems
possible that virus-encoded IL-6 contributes to malignant growth of HHV-8-pos. B-cell lymphatic tumors. We have tested a
preparation of HHV-8-derived IL-6 for the ability to promote the proliferation of the human myeloma cell line INA-6, which is
strictly dependent on exogenous IL-6 for growth and survival. Viral IL-6 significantly induced DNA

synthesis of INA-6 cells, but required much more protein on a weight basis when compared with hIL-6 for maximal proliferation. The proliferative effect of vIL-6 was almost completely inhibited by a combination of anti-IL-6 receptor (IL-6R) and anti-gp130 antibodies or IL-6R superantagonist Sant7 and anti-gp130 antibodies. This report demonstrates that vIL-6 has proliferative activity on human cells and that the IL-6R and gp130 are involved in vIL-6 signaling in the myeloma cell line INA-6.

L11 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:760040 CAPLUS
DN 126:55664
TI Human herpesvirus 8 encodes a homolog of interleukin-6
SO Journal of Virology (1997), 71(1), 839-842
CODEN: JOVIAM; ISSN: 0022-538X
AU Neipel, Frank; Albrecht, Jens-Christian; Ensser, Armin; Huang, Yao-Qi; Li, Jian Jun; Friedman-Kien, Alvin E.; Fleckenstein, Bernhard
AB Kaposi's sarcoma is a multifocal lesion that is reported to be greatly influenced by cytokines such as interleukin-6 (IL-6) and oncostatin M. DNA sequences of a novel human gammaherpesvirus, termed human herpesvirus 8 (HHV-8) or Kaposi sarcoma-associated herpesvirus, have been identified in all epidemiol. forms of Kaposi's sarcoma with high frequency. The presence of HHV-8 DNA is also clearly associated with certain B-cell lymphomas (body cavity-based lymphomas) and multicentric Castleman's disease. Sequence anal. of a 17-kb fragment revealed that adjacent to a block of conserved herpesvirus genes (major DNA-binding protein, glycoprotein B, and DNA polymerase), the genome of HHV-8 encodes structural homolog of IL-6. This cytokine is involved not only in the pathogenesis of Kaposi's sarcoma but also in certain B-cell lymphomas and multicentric Castleman's disease. The viral counterpart of IL-6 (vIL-6) has conserved important features such as cysteine residues involved in disulfide bridging or an amino-terminal signal peptide. Most notably, the region known to be involved in receptor binding is highly conserved in vIL-6. This conservation of essential features and the remarkable overlap between diseases associated with HIV-8 and diseases associated with IL-6 dysregulation clearly suggest that vIL-6 is involved in HHV-8 pathogenesis.

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L3 111 S L1 (L) L2
L4 40 DUP REM L3 (71 DUPLICATES REMOVED)
L5 1 S L4 AND PY<=1996
L6 40 FOCUS L4 1-

=> d an ti so au ab pi l6 38 21 17 1

L6 ANSWER 38 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN

AN 1998:89360 CAPLUS

DN 128:166368

TI The interleukin 6 of human herpesvirus 8 and its use in diagnostics and therapeutics

SO PCT Int. Appl., 19 pp.

CODEN: PIXXD2

IN Fleckenstein, Bernhard; Albrecht, Jens-Christian; Neipel, Frank;

Friedman-Kien, Alvin; Huang, Yao-Qi

AB Human herpesvirus 8 is found to carry a gene for an interleukin 6 that can bind to the interleukin 6 receptor. The interleukin and the gene encoding can be used in the diagnosis and treatment of a number of diseases including: Kaposi sarcoma, Castleman's disease, multiple myeloma, kidney cell carcinoma, mesangial proliferative glomerulonephritis or B cell lymphoma. The protein may be manufactured by expression of the cloned gene.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 9803657	A1	19980129	WO 1996-EP3199	19960719
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W: US

RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

EP 912742	A1	19990506	EP 1996-927558	19960719
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R: AT, BE, CH, DE, ES, FR, GB, IT, LI, LU, NL, SE

US 2004228838	A1	20041118	US 2004-828343	20040421
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L6 ANSWER 21 OF 40 MEDLINE on STN

AN 97138401 MEDLINE

TI Human herpesvirus 8 encodes a homolog of interleukin-6.

SO Journal of virology, (1997 Jan) 71 (1) 839-42.

Journal code: 0113724. ISSN: 0022-538X.

AU Neipel F; Albrecht J C; Ensser A; Huang Y Q; Li J J; Friedman-Kien A E; Fleckenstein B

AB Kaposi's sarcoma is a multifocal lesion that is reported to be greatly influenced by cytokines such as interleukin-6 (IL-6) and oncostatin M. DNA sequences of a novel human gammaherpesvirus, termed human herpesvirus 8 (HHV-8) or Kaposi sarcoma-associated herpesvirus, have been identified in all epidemiological forms of Kaposi's sarcoma with high frequency. The presence of HHV-8 DNA is also clearly associated with certain B-cell lymphomas (body cavity-based lymphomas) and multicentric Castleman's disease. Sequence analysis of a 17-kb fragment revealed that adjacent to a block of conserved herpesvirus genes (major DNA-binding protein, glycoprotein B, and DNA polymerase), the genome of HHV-8 encodes structural homolog of IL-6. This cytokine is involved not only in the pathogenesis of Kaposi's sarcoma but also in certain B-cell lymphomas and multicentric Castleman's disease. The viral counterpart of IL-6 (vIL-6) has conserved important features such as cysteine residues involved in disulfide bridging or an amino-terminal signal peptide. Most notably, the region known to be involved in receptor binding is highly conserved in vIL-6. This conservation of essential features and the remarkable overlap between diseases associated with HHV-8 and diseases associated with IL-6 dysregulation clearly suggest that vIL-6 is involved in HHV-8 pathogenesis.

L6 ANSWER 17 OF 40 MEDLINE on STN
AN 2003592109 MEDLINE
TI Molecular mechanisms for viral mimicry of a human cytokine: activation of gp130 by HHV-8 interleukin-6.
SO Journal of molecular biology, (2004 Jan 9) 335 (2) 641-54.
Journal code: 2985088R. ISSN: 0022-2836.
AU Boulanger Martin J; Chow Dar-chone; Brevnova Elena; Martick Monika; Sandford Gordon; Nicholas John; Garcia K Christopher
AB Kaposi's sarcoma-associated herpesvirus (KSHV, or HHV-8) encodes a pathogenic viral homologue of human interleukin-6 (IL-6). In contrast to human IL-6 (hIL-6), viral IL-6 (vIL-6) binds directly to, and activates, the shared human cytokine signaling receptor gp130 without the requirement for pre-complexation to a specific alpha-receptor. Here, we dissect the biochemical and functional basis of vIL-6 mimicry of hIL-6. We find that, in addition to the "alpha-receptor-independent" tetrameric vIL-6/gp130 complex, the viral cytokine can engage the human alpha-receptor (IL-6Ralpha) to form a hexameric vIL-6/IL-6Ralpha/gp130 complex with enhanced signaling potency. In contrast to the assembly sequence of the hIL-6 hexamer, the preformed vIL-6/gp130 tetramer can be decorated with IL-6Ralpha, post facto, in a "vIL-6-dependent" fashion. A detailed comparison of the viral and human cytokine/gp130 interfaces indicates that vIL-6 has evolved a unique molecular strategy to interact with gp130, as revealed by an almost entirely divergent structural makeup of its receptor binding sites. Viral IL-6 appears to utilize an elegant combination of both convergent, and unexpectedly divergent, molecular strategies to oligomerize gp130 and activate similar downstream signaling cascades as its human counterpart.

L6 ANSWER 1 OF 40 MEDLINE on STN
AN 2001198464 MEDLINE
TI Detection of direct binding of human herpesvirus 8-encoded interleukin-6 (vIL-6) to both gp130 and IL-6 receptor (IL-6R) and identification of amino acid residues of vIL-6 important for IL-6R-dependent and -independent signaling.
SO Journal of virology, (2001 Apr) 75 (7) 3325-34.
Journal code: 0113724. ISSN: 0022-538X.
AU Li H; Wang H; Nicholas J
AB Human herpesvirus 8 (HHV-8) is associated with Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease; in all of these diseases, interleukin-6 (IL-6) has been implicated as a likely mitogenic and/or angiogenic factor. HHV-8 encodes a homologue of IL-6 (viral IL-6 [vIL-6]) that has been shown to be biologically active in several assays and whose activities mirror those of its mammalian counterparts. Like these proteins, vIL-6 mediates its effects through the gp130 signal transducer, but signaling is not dependent on the structurally related IL-6 receptor (IL-6R; gp80) subunit of the receptor-signal transducer complex. However, as we have shown previously, IL-6R can enhance vIL-6 signal transduction and can enable signaling through a gp130 variant (gp130.PM5) that is itself unable to support vIL-6 activity, indicating that IL-6R can form part of the signaling complex. Also, our analysis of a panel of vIL-6 mutants in transfection experiments in Hep3B cells (that express IL-6R and gp130) showed that most were able to function normally in this system. Here, we have used in vitro vIL-6-receptor binding assays to demonstrate direct binding of vIL-6 to both gp130 and IL-6R and vIL-6-induced gp130-IL-6R complex formation, and we have extended our functional analyses of the vIL-6 variants to identify residues important for IL-6R-independent and IL-6R-dependent signaling through native gp130 and gp130.PM5, respectively.

These studies have identified residues in vIL-6 that are important for IL-6R-independent and IL-6R-mediated functional complex formation between vIL-6 and gp130 and that may be involved directly in binding to gp130 and IL-6R.